REMARKS

The Official Action dated June 4, 2003 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, the claims have been amended for various matters of form and clarity. Claim 1 has also been amended to recite that the method is for determining the concentration of an analyte in the sample, as set forth in the specification at page 1, lines 3-5 and page 2, lines 30-32, and to recite that the analyte/receptor complex is labeled in the isolated fraction as disclosed in the specification, for example at page 5, lines 27-32. Claim 25 has also been amended to clarify that the first amount of analyte-binding receptor reagent is not immobilized on the solid phase member as set forth in the specification, for example at page 4, lines 17-23. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, the Examiner rejected claims 1-10, 12-18, 25-28, 37 and 38 under 35 U.S.C. §112, second paragraph, as being indefinite. In claim 1, the Examiner asserted that use of a label must be recited. The Examiner also asserted that the preamble should recite determining "the concentration of" an analyte in a sample and that recitation of a known amount of receptor should be made in step (a). Finally, the Examiner questioned what fraction is isolated on the solid phase. The Examiner questioned the meaning of "minor fraction" in claim 7, asserted insufficient basis for recitation of "the detection reagent" in claims 14 and 15, and asserted insufficient antecedent basis for the term "said second amount" in claim 25 and the claims depending from claim 25.

However, Applicants submit that claims 1-10, 12-18, 25, 27, 28, 37 and 38 as presented herein are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Initially, Applicants note that claim 1 recites a method of determining the concentration of an analyte in a sample. As set forth in the specification, the concentration may be determined, for example, quantitatively, semi-quantitatively or qualitatively. Claim 1 also clearly recites that the sample is contacted with a known amount of receptor and that the analyte/receptor complex is labeled. As set forth in the specification at page 5, label refers to any substance which is capable of producing a signal that is detectable by visual or instrumental means. The term "minor fraction" has been omitted from claim 7, and the dependency of claims 14 and 15 has been changed to claim 10 to provide proper antecedent basis for the terms therein. Finally, claim 25 clearly recites first and second amounts of the analyte-binding receptor reagent to provide proper antecedent basis for these terms in claim 25 and the claims dependent thereon. It is therefore submitted that the claims are definite and that the rejection under 35 U.S.C. §112, second paragraph, is overcome. Reconsideration is respectfully requested.

Claims 1, 3, 7, 10-14, 31 and 32 were rejected under 35 U.S.C. §102(b) as being anticipated by the Sommer U.S. Patent No. 5,569,608. The Examiner asserted that Sommer discloses a method for determining the concentration of analyte in a test fluid by contacting the test fluid with an excess of anti-hsa:gold sol conjugate (receptor) and a solid phase which captures analyte/receptor on one section and also captures unreacted receptor on another section, thus fractionating the receptor.

However, as set forth in detail below, Applicants submit that the methods of determining the concentration of an analyte in the sample defined by claims 1, 3, 7, 10, 12-14, 31 and 32 are not anticipated by, and are patentably distinguishable from, Sommer. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

As defined by claim 1, the invention is directed to a method for determining the concentration of an analyte in a sample. The present methods are particularly suitable for determining the concentration of an analyte in a sample containing a high concentration of the analyte, without the need for dilution of the sample or use of excessive amounts of capturing and labeled detection reagents. Thus, the present methods provide improvements in convenience and cost as compared with prior art methods for measuring high concentrations of analyte in a sample.

According to claim 1, the method comprises contacting the sample with a known amount of a receptor which binds specifically to the analyte to form an analyte/receptor complex, wherein the known amount of receptor is in excess of an amount of receptor required to bind all analyte in the sample. A fraction of receptor which is contacted with the analyte is then isolated on a solid phase. The resulting isolated fraction of receptor contacted with analyte includes both analyte/receptor complex and unreacted receptor, and the ratio between receptor in the isolated fraction (both complexed and unreacted) and the known amount of receptor contacted with the sample is in a range of from about 1:2 to about 1:1000. The analyte/receptor complex in the isolated fraction is then labeled and the amount of labeled analyte/receptor complex in the isolated fraction is then detected. From the detected amount of labeled analyte/receptor complex, the concentration of analyte in the sample is determined. As will be apparent, only a fraction of analyte, namely that contained in the isolated fraction, is isolated and labeled, thereby allowing use of lower amounts of, for

example, immobilizing and labeling reagents than would be required if all analyte in the sample was, for example, immobilized and labeled.

Sommer discloses a method for determining the concentration of analyte in the test fluid by immunochromatography techniques. As described at column 2, beginning at line 19, a test strip has a first region containing mobile specific binding partner bearing a detectable label for reaction with an analyte, and a second region containing an immobilized analyte or analog thereof. An analyte-containing sample is applied and the analyte present in the sample binds to the labeled specific binding partner to form a complex, with excess, unreacted labeled binding partner free to further react when the sample carries the analyte/labeled binding partner conjugate and unreacted labeled binding partner to a second region. In the second region, unreacted labeled binding partner binds to the immobilized analyte in inverse relationship to the concentration of analyte in the fluid test sample. The strip may optionally include a third region which contains means for immobilizing the complex formed between the analyte and the labeled binding partner.

In the Sommer method, all of the analyte in the sample is reacted with the labeled binding partner. In contrast, in the present method, only the portion of analyte/receptor complex in the isolated fraction is labeled. This is a significant difference, particularly for samples having high concentrations of analyte, as the amount of label can be significantly reduced according to the present methods. Moreover, in the Sommer method, all unreacted labeled binding partner is immobilized and measured in the second region while, optionally, all analyte-labeled binding partner conjugate is immobilized and measured in the third region. In contrast, in the method of claim 1, a fraction including both analyte/receptor complex and unreacted receptor is isolated on a solid phase and the analyte/receptor complex in the isolated fraction is labeled.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q.2d 1949, 1950 (Fed Cir. 1999). In view of the failure of Sommer to disclose a method as defined in claim 1, wherein only that portion of the analyte/receptor complex in an isolated fraction of receptor contacted with the analyte is labeled, and the failure of Sommer to disclose a method as defined in claim 1 wherein a fraction including both analyte/receptor complex and unreacted receptor is isolated on a solid phase, Sommer fails to disclose each and every element as set forth in the claims. Thus, Sommer does not anticipate the presently claimed methods under 35 U.S.C. §102. It is therefore submitted that the rejection of claims 1, 3, 7, 10, 12-14, 31 and 32 under 35 U.S.C. §102 based on Sommer has been overcome. Reconsideration is respectfully requested.

Claims 19, 22, 24, 25, 27, 28 and 33-38 were rejected under 35 U.S.C. §103 as unpatentable over Sommer in view of the Bayer et al "Immunoassay" publication, the Maggio "Enzyme-Immunoassay" publication and the Boguslaski et al U.S. Patent No. 5,420,016. The Examiner relied on Bayer et al as disclosing avidin-biotin systems used in immunoassays, on Maggio as disclosing immunoassay performed with a solid phase, and on Boguslaski et al as disclosing test kits.

However, as set forth below, Applicants submit that the kits defined by claims 19, 22, 24, 25, 27, 28 and 33-38 are nonobvious over and patentably distinguishable from Sommer in view of Bayer et al, Maggio and Boguslaski et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Independent claims 19, 22 and 25 are directed to test kits for determining an analyte in a sample. According to claim 19, the test kit comprises a receptor reagent having a first part which binds specifically to the analyte, and a solid phase member having immobilized

thereon a ligand which binds specifically to a second part of the receptor reagent. The receptor-binding capacity of the ligand immobilized on the solid phase member is less than the ligand-binding capacity of the receptor reagent. The ratio between the receptor-binding capacity of ligand immobilized on the solid phase and the ligand-binding capacity of the analyte-specific receptor reagent is in a range of from about 1:2 to about 1:100.

According to claim 22, the test kit comprises a receptor reagent having a first part which binds specifically to the analyte, wherein only a fraction of the receptor reagent has a second part which binds to a specific ligand. The ratio between ligand-binding analyte-specific receptor reagent and analyte-specific receptor reagent is in a range of from about 1:2 to about 1:100. The test kit further comprises a solid phase member having the specific ligand immobilized thereon.

Finally, according to claim 25, the test kit comprises a first amount of an analyte-binding receptor reagent, and a solid phase member having immobilized thereon a second amount of the analyte-binding receptor reagent. The first amount of analyte-binding receptor reagent is not immobilized on the solid phase member. The ratio between the second amount of analyte-binding receptor reagent immobilized to the solid phase and the first and second amounts of analyte-binding receptor reagent together is in a range of from about 1:2 to about 1:100.

The test kits of claims 19, 22 and 25 are not anticipated by the teachings of Sommer. As noted above, Sommer discloses a test strip wherein the first region contains mobile specific binding partner, the second region contains an immobilized analyte or analog thereof for binding all non-conjugated labeled specific binding partner, and, optionally, the third region contains means for immobilizing the complex formed between all analyte in the sample and the labeled binding partner. However, Applicants find no teaching in Sommer of

test kits as defined in claims 19 and 22, comprising a receptor reagent having a first part which binds specifically to an analyte and a second part to which a ligand, immobilized on a solid phase member, binds specifically. In fact, if such a receptor was used as the labeled binding partner in Sommer, both analyte-labeled binding partner conjugate and free labeled binding partner would be immobilized in the second region of the Sommer test strip, thereby providing an inaccurate measurement. Additionally, Applicants find no teaching or suggestion by Sommer relating to a test kit as defined in claim 25 comprising first and second amounts of analyte-binding receptor reagent which respectively are not immobilized on a solid phase member and, conversely, immobilized on the solid phase member. Rather, the test strip of Sommer only comprises mobile labeled binding partner in the first region. In fact, use of immobilized analyte-binding receptor reagent in the Sommer test strip would result in inaccurate measurements in the second and third regions.

Moreover, the deficiencies of Sommer are not resolved by the secondary references. While Bayer et al disclose in detail an avidin-biotin system in immunoassays, Applicants find no teaching or suggestion in this reference relating to test kits as defined by claims 19, 22 or 25. Similarly, Applicants find no teaching or suggestion by Bayer et al which would motivate one of ordinary skill in the art to modify the teachings of Sommer to result in test kits as presently claimed. In fact, any such modifications would be contrary to the teachings of Sommer since, as noted above, modification of the Sommer device to include the elements of claims 19, 22 or 25 would result in the inoperability of the Sommer device.

Similarly, while Maggio discloses immunoassays performed with a solid phase, and Boguslaski et al disclose test kits in general, Applicants find no teaching or suggestion in either of these references of test kits comprising the elements of claims 19, 22 or 25, or any motivation for modifying the teachings of Sommer to provide test kits as presently claimed.

Moreover, none of the cited references teach or suggest that test kits as presently claimed are advantageous for determining the concentration of an analyte in a sample having a high concentration of the analyte or the improvements in convenience and cost provided by the test kits as presently claimed.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). Moreover, obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination, *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987). In view of the deficiencies of Sommer and the secondary references discussed above, and the failure of any of these references to teach or suggest modification of the Sommer test strip along the lines of the present invention, and any desirability of such a modification, the combination of references does not render the presently claimed test kits obvious. It is therefore submitted that the test kits defined by claims 19, 22, 24, 25, 27, 28 and 33-38 are nonobvious over Sommer in view of Bayer et al, Maggio and Boguslaski et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Claims 2, 8, 9, 16, 29 and 30 were rejected under 35 U.S.C. §103 as unpatentable over Sommer in view of Bayer et al. The Examiner asserted it would have been obvious to biotintilate the receptor of Sommer and incorporate avidin as taught by Bayer et al.

However, Applicants submit that the methods defined by claims 2, 8, 9, 16, 29 and 30 are nonobvious over and patentably distinguishable from the combination of Sommer and Bayer et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

Claims 2, 8, 9, 16, 29 and 30 depend directly or indirectly from claim 1. The deficiencies of Sommer with respect to claim 1 are discussed in detail above and apply equally with respect to claims 2, 8, 9, 16, 29 and 30. Particularly, Sommer provides no teaching or suggestion of a method as defined in claim 1 wherein only a fraction of receptor contacted with analyte is isolated on a solid phase and the isolated fraction of analyte-receptor complex is labeled. To the contrary, Sommer discloses labeling all analyte and immobilizing all unconjugated labeled specific binding partner in a second region, with optional immobilization of all labeled analyte in a third region. These deficiencies in the teachings of Sommer are not resolved by Bayer et al. As noted above, Bayer et al disclose avidin-biotin systems, but Applicants find no teaching or suggestion by Bayer et al relating to a method as defined in claim 1 or for modifying the teachings of Sommer to result in such a method. Thus, the combination of Sommer and Bayer et al do not provide an enabling disclosure of the claimed methods and therefore do not render the methods of these claims obvious. It is therefore submitted that the methods defined by claims 2, 8, 9, 16, 29 and 30 are nonobvious over and patentably distinguishable from Sommer in combination with Bayer et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Finally, claims 4-6 were rejected under 35 U.S.C. §103 as unpatentable over Sommer in view of the Hossom et al U.S. Patent No. 4,623,461, while claim 15 was rejected under 35 U.S.C. §103 as unpatentable over Sommer in view of the Singer et al U.S. Patent No. 5,573,909. The Examiner relied on Hossom et al as disclosing a technique of contacting a sample with a liquid phase containing a receptor prior to contact with a solid phase and on Singer et al as disclosing fluorophore labels. Claims 17 and 18 were rejected under 35 U.S.C.

§103 as unpatentable over Sommer in view of the Guan et al U.S. Patent No. 6,316,205. The Examiner relied on Guon et al as disclosing sandwich immunoassay.

However, Applicants submit that the methods defined by claims 4-6, 15, 17 and 18 are nonobvious over and patentably distinguishable from Sommer in view of any of Hossom et al, Singer et al and Guon et al. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

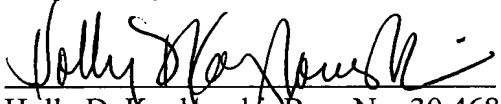
Each of claims 4-6, 15, 17 and 18 depend directly or indirectly from claim 1. The deficiencies of Sommer with respect to claim 1 are discussed in detail above and apply equally as well with respect to claims 4-6, 15, 17 and 18. Moreover, these deficiencies in the teachings of Sommer are not resolved by any of Hossom et al, Singer et al or Guon et al. For example, Hossom et al disclose a transverse flow diagnostic device for use with any of the conventional procedures used for analyte assays (column 2, lines 31-33). Even if the method taught by Sommer were to employ a liquid phase as taught by Hossom et al, such a modification does not resolve the noted deficiencies of Sommer with respect to claim 1. That is, such a method would still require reaction of all analyte with a labeled specific binding partner and immobilization of all unreacted labeled specific binding partner in the second region, optionally with immobilization of all labeled analyte in a third region, contrary to the method of claim 1.

Singer et disclose fluorescent labels using microparticles with controllable stokes shift. However, the deficiencies of Sommer noted above are not resolved by use of fluorescent labeling particles as taught by Singer et al. Finally, Guon et al disclose the use of a blood sample. However, if a whole blood sample were to be employed in the method of Sommer, such a modification does not result in, or teach or suggest the advantages of, the presently claimed methods for determining the concentration of an analyte in a sample.

Accordingly, the methods of claim 1, and claims 4-6, 15, 17 and 18 dependent thereon, are nonobvious over and patentably distinguishable from Sommer in view of any of Hossom et al, Singer et al and Guon et al. It is therefore submitted that the rejections of these claims under 35 U.S.C. §103 have been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the rejections under 35 U.S.C. §§ 102, 103 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,



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